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Prague, June 11, 2004

European Patent Office
D-80298 Munich

Re: **PCT Patent Application No. PCT/CZ03/00046**
Reply to the First Written Opinion
Applicant: **PLIVA-LACHEMA**
Title: **BIODEGRADABLE COMPOSITION WITH PROLONGED RELEASE OF THE BIOLOGICAL ACTIVE COMPOUND AND PREPARATION THEREOF**

Your ref.: PCT/CZ03/00046
Our ref.: 150371/KR

Dear Sirs,

The Written Opinion has mentioned the following prior art documents as being allegedly relevant when appreciating the novelty and the inventive step of the matter claimed in the present application:

D1= HAMPL JAROSLAV ET AL: "Adjuvant activity of linear aliphatic polyester and branched aliphatic oligoester microspheres", INTERNATIONAL JOURNAL OF PHARMACEUTICS, (1996), 144(1), 107-114;

D2= SK 279 067 B (HALKOVA LENKA; VACKOVA MARIE (CZ), BUCHTA VLADIMIR (CZ); DITTRICH), 3 June 1998;

D3= US 5 783 205 A (MARKS SUSAN M ET AL), 21 July 1998;

D4= EP 0 290 983 A (HENKEL KGAA), 17 November 1988;

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D5= US 5 143 730 A (FUES JOHANN-FRIEDRICH ET AL), 1 September 1992;

D6= US 6 420 454 B1 (WENZ ROBERT ET AL), 16 July 2002.

In order to render the subject matter of the present application free of the above-listed prior art, we have redrafted the claims as originally on file by (1) combining the original claims 1, 2 and 6 into a new claim 1 with restricting the application way of the claimed composition therein to the administration into tissues, only, (2) leaving out claims 3 to 5, and (3) adequately renumbering the original claims 7 to 11 as new claims 2 to 6, respectively. Once it being so, the new claims 1 to 6 read as follows (see also annexed substitute sheets 18 and 19):

1. Biodegradable antitumour composition with prolonged release of an antitumour agent destined for the administration into tissues, characterised in that it comprises at least one antitumour agent and a carrier, consisting of biodegradable oligoester, having the numeric mean relative molecular mass M_n from 650 to 7 500, the mass mean relative molecular mass M_w from 800 to 10 000 and the glass transition temperature T_g from -35 to 45 °C, and which is prepared by polycondensation reaction of polyhydric alcohol containing at least 3 hydroxy groups with at least one aliphatic α -hydroxy acid in the molar ratio of polyhydric alcohol to aliphatic α -hydroxy acid being from 0.5:99.5 to 12:88, wherein the central molecule of biodegradable oligoester is a polyhydric alcohol, to the hydroxy groups of which chains created from several molecules of at least one aliphatic α -hydroxy acid are bound by ester bonds, and in that it is in the form of homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion.

2. The composition according to claim 1, characterised in that it further comprises at least one liquid biocompatible plasticizer, wherein the weight ratio of at least one biocompatible plasticizer to biodegradable oligoester is from 1:20 to 9:10.

3. The composition according to claim 2, characterised in that the liquid biocompatible plasticizer is soluble in the carrier and imperfectly soluble or insoluble in water.

4. The composition according to claims 1 to 3, characterised in that it further comprises at least one agent influencing the kinetics of the release of the antitumour agent.

5. The composition according to claim 1 to 4, characterised in that it further comprises at least one stabilizer of the antitumour agent or carrier.

6. The preparation of the antitumour composition according to claims 1 to 5, characterised in that an antitumour agent, a carrier, and optionally a liquid biocompatible plasticizer, an agent influencing the kinetics of the release of the antitumour agent, a stabilizer of the antitumour agent or a stabilizer of the carrier are heated to the temperature of 35 to 75 °C and mixed.

The support for such an amendment of the claims consists in that the new combination of the original claims 1, 2 and 6 narrows the invention scope in view of that disclosed in the original claim 1 and thus this combination does not exceed the original file at all. As far as the complement "destined for the administration into tissues" as added into preamble to the new claim 1 is concerned, this finds support in the present example 6 wherein (see line 11 of page 17) an intratumoral administration is expressly mentioned.

Both the novelty and inventive step of the invention matter as presently claimed in the new claims 1 to 6 over the prior art documents D1 to D6 are going to be evident from the following comments, respectively:

The document **D1** describes **microspheres** prepared of terpolymer of DL-lactic acid, glycolic acid and mannitol, copolymer of DL-lactic acid and mannitol and two lactido-glycolide copolymers by **solvent evaporation emulsion technique**. Generally, the microspheres represent

release systems having a particle structure wherein the individual fractions of the active matter contained in the individual microspheres are discretely separated from each other by either a gaseous phase (air) if administered on their own or a liquid medium if administered as a liquid formulation. Moreover, the microspheres have incorporated in their surface sheet a polymer emulsifier and residual solvents and each microsphere in addition shows a heterogeneous structure composed of globe cavities produced by drying out an inner aqueous phase. At variance with the microspheres, the invention composition is a **plastic** (or ready to be rendered plastic) **monolithic system** (homogeneous one-phase solution, micellar colloid system, one-phase pr two-phase gel, suspension, paste or emulsion) wherein the active matter is directly and without any barrier scattered in a carrier (biodegradable oligoester). In accordance with this, the invention composition can be simply prepared by **mere heating** the active matter in presence of the carrier. As it is quite clear from the foregoing that the invention composition is, as to its structure, quite different from the prior art microspheres, the invention composition should be regarded as novel in view of the microspheres of D1.

The invention monolithic systems were recognised to swell and degrade by the hydrolysis of the ester bonds which produces both hydroxyl and carboxyl groups. The acid degradation products catalyse further degradation of the system. Such an autocatalytic impact of the degradation products on acid hydrolysis is influenced by their stay in the oligoester system. The stay time of the degradation products in the system is, in turn, dependent on the size of the system. In D1, there was no hint at all that would have instructed a person skilled in the art that the above desired release mechanism would have been in progress just as above outlined which appears to justify the inventive step of the invention composition in view of the microsphere system of D1. Taking into account that the individual microspheres are very small in size and represent so very small release systems, the hydrolysis of these microspheres systems proceeds, as distinct from the monolithic systems, without the catalytic effect of the

above-mentioned degradation products and so the release of active matters is in the case of microspheres systems more considerably influenced by their physico-chemical properties, such as solubility, distribution coefficient, sorption, and ionisation. Such a more important influence of the release kinetics on physico-chemical parameters of the microspheres can be explained by shorter diffusion path of the molecules or ions of the active matter that is for the microsphere systems shorter by factor 2 to 3. Taking into account the foregoing the invention composition should be taken for inventive in view of the microspheres of D1.

The document **D2** describes a particle composition obtained by 1) mixing a biodegradable oligoester with a combination of at least two antimicrobial agents, optionally in solution or in the molten state, 2) pressing thus reached solid blend, optionally after a preliminary solidification, and grinding the resulting solid block to a powder the particles of which are of 1 to 300 µm in size. This powder represents a release system having **particle structure** similar to that of the microspheres of R1 rather than that of the invention plastic monolithic system. As the particle composition of D2 is structurally different from the plastic monolithic system of the invention and there is, in D2, no hint leading the person skilled in the art obviously to the plastic monolithic system according to the invention, the latter should be considered as both novel and inventive over D2. All the detailed arguments supporting the novelty and inventiveness of the invention matter as mentioned in connection with D1 can be applied in connection with D2, as well.

The document **D3** provides a matrix material which can be used to deliver a drug, such as an antibiotic, into a diseased tissue **pocket**, such as a periodontal pocket. The material is preferably a boidegradable oligomer or polymer. The oligomer or polymer containing the drug is heated and is than delivered, preferably by injection, into the tissue pocket at a physiologically compatible temperature. Once the bioerodible material is injected into the pocket, the

material cools to the body temperature of the pocket. As it cools, the material hardens and remains in place in the tissue pocket. The hardened material bioerodes in the pocket and releases the drug over a period of several days. D3 also mentions (lines 25-27 of column 7) that a preferred group useful as matrix materials are oligomers of glycolic acid and/or lactic acid and their derivatives with mono- and/or polyfuncional alcohols. As the only specific method for preparing those preferred matrix materials the document D3 in fact teaches (lines 57-58 of column 6) **a synthesis from cyclic esters of lactic acids (lactones) realised by polymerising lactones while opening their cycle.** At variance with this, the biodegradable oligoesters according to the present invention are expressly prepared by **polycondensation reaction of polyhydric alcohol containing at least 3 hydroxy groups with at least one aliphatic α-hydroxy acid** (see the present claim 1). The both different preparative methods provide different final products taking into consideration the facts as coming after: 1) The thing is, the synthesis from the cyclic ester consists in polymerising the cyclic ester while opening the cycle thereof as already mentioned above. The polymerisation is the reaction that proceeds spontaneously and finishes by a termination. Consequently, in comparison with the product obtained by the polycondensation, as it is the case of the invention products, the products obtained by the polymerisation of D3 show **a broader distribution of molecular weights** and **a different (more random) arrangement of the constitutive units** in the copolymers. **This is not the case of the invention polycondensation reaction wherein both said distribution and arrangement can be controlled** taking profit from the possibility of terminating the polycondensation reaction when desired parameters are reached. 2) The products of the polymerisation contain a high proportion of non-reacted monomers that considerably influence the properties of thus obtained matrix materials, inclusive of an autocatalytic impact on the running of the biodegradation of the matrix material. Namely for a low molecular weight the content of the monomers and low molecular water-soluble components is very high. These undesirable substances must be therefore withdrawn, usually

by precipitating them from the solution. But this precipitation undesirably influences the polydisprsity of the matrix material since along with the monomers also a portion of less molecular fraction of the matrix material is eliminated. In addition, when precipitating the matrix materials are contaminated with the used solvents the elimination of which is hardly possible. **No such solvents are present in the invention biodegradable oligoesters.** 3) As distinct from the invention biodegradable oligoesters, the matrix materials of D3 prepared by the cycle-opening polymerisation in the presence of the polyhydric alcohols exhibit **a low branching rate** when having a low molecular weight. In such a case, the cyclic lactones react with the polyhydric alcohols, optionally with the acids. The polyhydric alcohols rather function as initiators as it was proved for pentaerythritol [Helminen, A., Korhonen, H., Seppälä, J.V., Polymer 42 (2001 3345] . With lower branching rate of the oligomers used in the framework of R3 the resulting oligoester material shows lower content of end hydroxyl groups that play key role in the mechanism of the degradation of the matrix carrier and thus influence the kinetics of the release of the active matter [De Jong, S.J. et al., Polymer 42 (2001), 2795] . **No such an effect occurs with the biodegradable oligoesters according to the invention.** As it clearly ensues from the foregoing that the invention composition comprises as a matrix carrier biodegradable oligoester being structurally and as to the presence of accompanying substances different from the carrier material disclosed in R3, the invention composition should be taken for novel over R3.

As the matrix material of D3 is expressly destined for the adminitration into open, periodontal, ophthalmic, or vaginal **pockets,** the **topical** rather than **intratissue administration** is in fact the case with D3. Taking into account that the topical administration is generally known to exhibit the release profile being quite different from that of the intratissue administration, a person skilled in the art could not have found out in D3 any hint that would have obviously instructed this person about that if a desired release profile after the intratissue administration has to be reached than the very

sophisticated biodegradable oligoesters as defined in the present application will have to be used as carrier material. Once it being so, the biodegradable antitumour composition according to the invention should be regarded as inventive against R3.

The documents **R4 to R6** disclose resorbable viscous to solid sealant for the mechanical stanching of blood on hard body tissue, particularly bones, based on oligomers of glycolic acid and/or lactic acid and derivatives thereof with monofunctional and/or polyfunctional alcohol and/or corresponding carboxylic acids. Nowhere in these documents, a composition comprising in addition to the sealant on its own an active matter to release is specifically mentioned. By this, the sealant compositions of D4 to D6 appear to be structurally different from the biodegradable antitumour composition according to the invention that, at variance with the sealants of D4 to D6, does comprise the active matter. The latter should be therefore considered as novel in view of R4 to R6.

As the matter as included in the documents R4 to R6 does not solve at all the problem of the controlled release of active substances, the person trying to solve such a problem could not have found out in D4 to D6 any hint that would have obviously lead this person to address the problem by using the sophisticated biodegradable oligoesters of the invention. So, the invention composition should be taken for inventive over D4 to D6.

Yours faithfully,

Jan Kubát
in the name of PLIVA-Lachema

Encl.: Substitute sheets 18, 19

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

TRAPLOVÁ ◆ HAKR ◆ KUBÁT
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WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	13/02/2004
Applicant's or agent's file reference: 150371/KB	REPLY DUE within 2 / 00 months/days from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CZ03/00046	15/08/2003	22/08/2002

International Patent Classification (IPC) or both national classification and IPC
A61K9/00

Applicant
PLIVA-LACHEMA A.S.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3.
For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 22/12/2004

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Form PCT/IPEA/408 (cover sheet) (march 2002)

I. Basis of the opinion

1. The basis of this written opinion is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

1. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claims references).

2. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.